UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,261	10/15/2001	David Y. Zhang	251305.0028 SBP/MCD	4119

7590 04/23/2007

Steven B. Pokotilow, Esq.
Stroock & Stroock & Lavan LLP
180 Maiden Lane
New York, NY 10038

EXAMINER	
LU, FRANK WEI MIN	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/978,261	ZHANG, DAVID Y.	
	Examiner	Art Unit	
	Frank W Lu	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/6/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's response to the office action filed on January 25, 2007 has been entered. The claims pending in this application are claims 40-44. Rejection and/or objection not reiterated from the previous office action are hereby withdrawn in view of the amendment filed on January 25, 2007.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 40-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 40 is rejected as vague and indefinite in view of step (b) (iii) because it is unclear what kind of signal is inhibited. Please clarify.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 40-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.*, (US Patent No. 5,942,391, published on August 24, 1999) in view of Wang *et al.*, (US Patent NO. 5,567,583, published on October 22, 1996) and Harris (US Patent No. 5,837,469, published on November 17, 1998).

Regarding claims 40 and 41since, in a method for detecting a target nucleic acid in a sample, Zhang *et al.*, teach: (a) contacting said nucleic acid in said sample in a reaction vessel under conditions that allow nucleic acid hybridization between complementary sequences in nucleic acids with oligonucleotide probes in the presence of paramagnetic particles coated with a ligand binding moiety, said oligonucleotide probes comprising one or more capture/amplification probes, each having a 3' nucleotide sequence that is neither complementary nor hybridizable to a nucleotide sequence in the target nucleic acid, and a 5' nucleotide sequence that is complementary and hybridizable to a nucleotide sequence in the target nucleic acid, or a 5' nucleotide sequence that is neither complementary nor hybridizable to a nucleotide sequence in the target nucleic acid, and a 3' nucleotide sequence that is complementary and hybridizable to a nucleotide sequence in the target nucleic acid, each capture/amplification probe further having a ligand bound to the non-complementary sequence of the probe, wherein said ligand is capable of binding to and forming an affinity pair with said ligand binding moiety coated onto said paramagnetic particles; said oligonucleotide probes further comprising a circularizable amplification probe having 3' and 5' regions that are complementary to adjacent but noncontiguous sequences in the target nucleic acid, said 3' and 5' regions separated by a linker region that is neither complementary nor hybridizable to a nucleotide sequence in the target nucleic acid, such that a complex is formed comprising the target nucleic acid, circularizable

probe, capture/amplification probes and paramagnetic particles, wherein the capture/amplification probes are hybridized to the complementary nucleotide sequences in the target nucleic acid and are bound to the paramagnetic particles through the binding of the ligand on the capture/amplification probe to the ligand binding moiety on the paramagnetic particles, and the circularizable probe is bound on its 3' and 5' ends to adjacent but noncontiguous sequences in the target nucleic acid; and (c) ligating the 3' and 5' ends of said circularizable probe with a ligating agent that joins nucleotide sequences such that a circular amplification probe is formed (see claim 1 in columns 67-69 and Figures 1 and 7), Zhang *et al.,* disclose that the circular oligonucleotide probe is formed by ligating the 3' and 5' ends of a linear oligonucleotide probe (ie., an oligonucleotide probe taught by Zhang *et al.,*) comprising 3' and 5' regions complementary to adjacent sequences in the target nucleic acid under conditions that allow hybridization between complementary sequences in the target nucleic acid and the linear oligonucleotide probe as recited in claim 41. Since, since Zhang *et al.,* teach that, after the circular oligonucleotide probe is formed, the circular oligonucleotide probe contacts with the target nucleic acid, Zhang *et al.,* disclose contacting the nucleic acid with a circular oligonucleotide probe under conditions that allow hybridization between complementary sequences in the target nucleic acid and the circular oligonucleotide probe as recited in (a) of claim 40. Since, in a method for detecting a target nucleic acid in a sample, Zhang *et al.,* further teach: (d) amplifying said circular amplification probe by contacting said complex with a first extension primer that is complementary and hybridizable to a portion of the linker region of the circular amplification probe and a second extension primer that is substantially identical to a portion of the linker region of the circular amplification probe that does not overlap with the

portion of the linker region to which the first extension primer is complementary, dNTPs, and a DNA polymerase having strand displacement activity, under conditions whereby the first extension primer is extended around the circle for multiple revolutions to form a single stranded DNA of repeating units complementary to the sequence of the circular probe, and multiple copies of the second extension primer hybridize to complementary regions of the single stranded DNA and are extended by the DNA polymerase to provide extension products, and whereby the extension products of the second extension primers displace downstream copies of the second extension primers and corresponding extension products of said downstream copies to provide displaced single strands to which multiple copies of said first extension primer bind and are extended by the DNA polymerase; (e) allowing said amplification to proceed until multiple copies of double stranded amplified DNA of varying lengths are produced; and (f) detecting said amplified DNA, wherein detection thereof indicates the presence of the target nucleic acid in the clinical sample (see claim 1 in columns 67-69) and amplification is ramification-extension amplification method (RAM) and is performed in an isothermal condition (see column 6, first paragraph and column 22, lines 52-60), Zhang *et al.,* disclose adding a first primer wherein the first primer comprises (A) a first sequence that is complementary to the circular probe as recited in b) of claim 40, adding a DNA polymerase as recited in c) of claim 40, and amplifying the circular probe using ramification-extension amplification method (RAM) under isothermal conditions and detection indicates the presence of the target nucleic acid in the sample as recited in d) of claim 40,

Zhang *et al.,* do not disclose adding a primer pair comprising a first primer and a second

primer wherein (i) the first primer of the pair comprises (A) a first sequence that is complementary to the circular probe, (B) a second sequence that is complementary to the second primer of the pair, and (C) a signal generating moiety; (ii) the second primer of the pair comprises (A) a sequence that is complementary to the first primer and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and (iii) when the first primer and the second primer are bound to one another, the signal is inhibited as recited in (b) of claim 40, and detecting an increase in the signal which is generated by separating the signal generating moiety and the quenching, masking or inhibitory moiety as recited in (d) of claim 40, and disclose that the signal generating moiety is a fluorescent agent as recited in claim 42.

Wang *et al.,* teach adding a primer pair comprising a first primer and a second primer wherein (i) the first primer of the pair comprises (A) a first sequence that is complementary to the circular probe, (B) a second sequence that is complementary to the second primer of the pair, and (C) a signal generating moiety; (ii) the second primer (ie., the oligonucleotide which is incapable of acting as a primer for said polymerase of the pair taught by Wang *et al.,*) comprises (A) a sequence that is complementary to the first primer and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and (iii) when the first primer and the second primer are bound to one another, the signal is inhibited as recited in (b) of claim 40 and also teach that the signal generating moiety is a fluorescent agent as recited in claim 42 (see column 3, second paragraph, columns 19 and 20, claims 1 and 3, and Figure 1). Since the word "isothermal" is defined as "[O]f, relating, to, or registering equal temperature" (see

WEBSTER'S II New Riverside University Dictionary, page 647) and there is no definition for "ramification-extension amplification" in the specification, the extension step of the amplification reaction taught by Wang *et al.,* is considered to be performed in an isothermal condition (ie., 72°C for 60 seconds) and the amplification reaction taught by Wang *et al.,* is considered as a ramification-extension amplification method as recited in step d) of claim 40.

Since Harris teaches that an increase in donor fluorescence intensity or a decrease in acceptor fluorescence intensity is detected and/or monitored as an indication that target amplification is occurring or has occurred (see column 8, first paragraph and column 9, second paragraph), Harris discloses detecting an increase in the signal (ie., an increase in donor fluorescence intensity) which is generated by separating the signal generating moiety and the quenching, masking or inhibitory moiety as recited in (d) of claim 40.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 40 wherein (i) the first primer of the pair comprises (A) a first sequence that is complementary to the circular probe, (B) a second sequence that is complementary to the second primer of the pair, and (C) a signal generating moiety; (ii) the second primer comprises (A) a sequence that is complementary to the first primer and (B) a moiety capable of quenching, masking or inhibiting the activity of the signal generating moiety when located adjacent to, or in close proximity to the signal generating moiety; and (iii) when the first primer and the second primer are bound to one another, the signal is inhibited, and wherein an increase in the signal which is generated by separating the signal generating moiety and the quenching, masking or inhibitory moiety is detected in view of the patents of Zhang *et al.,* Wang *et al.,* and Harris. One having ordinary

skill in the art would have been motivated to do so because Wang *et al.,* have successfully detected the target nucleic acid in the sample by detecting a change in the signal which is generated by separating the signal generating moiety and the quenching, masking or inhibitory moiety and the simple replacement of one well known detection method (i.e., the method taught by Zhang *et al.,*) from another well known detection method (i.e., the method taught by Wang *et al.,*) during the process of detecting the target nucleic acid would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made since the detection method taught by Wang *et al..,* would eliminate or reduce nonspecific priming events (see column 7, second paragraph) and the detection method for detecting a decrease in acceptor fluorescence intensity taught by Wang *et al..,* and the method for detecting an increase in donor fluorescence intensity taught by Harris are used for the same purpose (ie., used as an indication that target amplification is occurring or has occurred or presence of target sequence) and are exchangeable (see column 8, first paragraph and column 9, second paragraph).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

7. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.,* in view of Wang *et al.,* and Harris as applied to claims 40-42, 45, and 46 above, and further in view of Heller (US Patent No. 5,532, 129, published on July 2, 1996).

The teachings of Zhang *et al.,* Wang *et al.,* and Harris have been summarized previously, *supra.*

Zhang *et al.,* Wang *et al.,* and Harris do not disclose that the signal generating moiety (ie., donor) is a chemiluminescent agent as recited in claim 43.

Heller teaches that either a fluorphore or a chemiluminescent group is used as a donor for non-radiative energy transfer (see column 3, second paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 43 wherein the signal generating moiety is a chemiluminescent agent in view of the patents of Zhang *et al.,* Wang *et al.,* Harris, and Heller. One having ordinary skill in the art would have been motivated to do so because Heller has successfully used a fluorphore or a chemiluminescent group as a donor for non-radiative energy transfer, and the simple replacement of one kind of signal generating moiety (i.e., a fluorescent donor taught by Wang *et al.,*) from another kind of signal generating moiety (i.e., chemiluminescent donor taught Heller) during the process of performing the method recited in claim 43 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because either a fluorphore or a chemiluminescent group is used as a donor for energy transfer and they are exchangeable (see Heller, column 3, second paragraph).

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06, 2144.07 and 2144.09.

Also note that there is no invention involved in combining old elements is such a manner that these elements perform in combination the same function as set forth in the prior art without giving unobvious or unexpected results. *In re Rose* 220 F.2d. 459, 105 USPQ 237 (CCPA 1955).

8. Claim 44 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang *et al.*, in view of Wang *et al.*, Harris, and Heller as applied to claims 40-43, 45, and 46 above, and further in view of Segev (US Patent No. 5, 437, 977, published on August 1, 1995).

The teachings of Zhang *et al.*, Wang *et al.*, Harris, and Heller have been summarized previously, *supra.*

Zhang *et al.*, Wang *et al.*, Harris, and Heller do not disclose that the signal generating moiety is an enzyme or enzyme substrate as recited in claim 44.

Segev teaches that non-radiative energy transfer is finished by a suitable chemiluminescent catalyst such as peroxidase and luciferase and a suitable absorber/emitter (see column 7, last paragraph and column 8, first paragraph).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 44 wherein the signal generating moiety is an enzyme in view of the patents of Zhang *et al.*, Wang *et al.*, Harris, Heller and Segev. One having ordinary skill in the art would have been motivated to do so because Segev has successfully used a suitable chemiluminescent catalyst such as peroxidase or luciferase and a suitable absorber/emitter for non-radiative energy transfer, and the simple replacement of one kind of chemiluminescent agent related non-radiative energy transfer method (i.e., the method taught by Heller) from another kind of chemiluminescent agent related non-

radiative energy transfer method (i.e., the method taught by Segev) during the process of performing the method recited in claim 44 would have been, in the absence of convincing evidence to the contrary, *prima facie* obvious to one having ordinary skill in the art at the time the invention was made because the method taught by Heller and the method taught by Segev are functional equivalent methods which are used for the same purpose.

Furthermore, the motivation to make the substitution cited above arises from the expectation that the prior art elements will perform their expected functions to achieve their expected results when combined for their common known purpose. Support for making the obviousness rejection comes from the M.P.E.P. at 2144.06.

Response to Arguments

In page 5, second paragraph bridging to page 7, first paragraph of applicant's remarks, applicant argues that "[A]pplicants have submitted a Petition for an Unintentionally Delayed Claim Under 37 CFR 1.78(a)(3) to claim benefit to prior-filed applications including Zhang. The Petition with a supporting Declaration and Exhibits is attached hereto for your convenience. If the Petition is granted, the subject application will claim priority to Zhang and thus Zhang will not be available as a 35 U.S.C. § 103(a) reference" and "[E]ven if Applicants' Petition is not granted Applicants respectfully disagree that it would have been obvious to perform the method recited in claim 40, in view of the patents of Zhang, Wang and Harris. Wang teaches the use of a blocking oligonucleotide which is designed to prevent primer extension of the bound primer. Therefore, even assuming the Wang primer/oligonucleotide pair binds to the target nucleic acid, primer extension will be prevented by the addition of the 'bulky molecular moiety...at the vicinity of the 3' end to sterically hinder the polymerase from catalyzing the extension reaction.'

(column 5, lines 25 - 27). Accordingly, it would not have been obvious to perform the method of claim 40 in the presence of a blocking oligonucleotide, which would only serve to compete with the second primer of the primer pair of the subject invention (i.e., the primer comprising a moiety capable of quenching, masking or inhibiting) and thereby block primer extension. Therefore, it would not have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to have performed the method recited in claim 40".

These arguments have been fully considered but they are not persuasive toward the withdrawal of the rejection. First, since the petition under 37 CFR 1.78(a)(3) is mismissed (see decision on petition mailed on March 16, 2007), "Zhang will not be available as a 35 U.S.C. § 103(a) reference" as argued by applicant is incorrect. Second, the statement "[W]ang teaches the use of a blocking oligonucleotide which is designed to prevent primer extension of the bound primer" argued by applicant is incorrect and nowhere in Wang *et al.,* teach such statement. In fact, Wang *et al.,* only state that "a blocking oligonucleotide which competes with non-specific priming sequences for hybridization to the primer. A blocking oligonucleotide of this invention is 'incapable of acting as a primer for polymerase', i.e., not able to act as a point of initiation for extension product synthesis. A blocking oligonucleotide can be rendered incapable of acting as a primer for an extension reaction by removing or modifying the 3' terminal hydroxyl group, e.g., addition of a terminal 3'-dideoxynucleotide, 3'-phosphorylation, 3'-amino termination and the conjugation of a bulky molecular moiety such as rhodamine at the vicinity of the 3' end to sterically hinder the polymerase from catalyzing the extension reaction" (see column 5, lines 14-27). Third, since the amplification reaction taught by Wang *et al.,* is performed in the presence of a first primer, a second primer and an oligonucleotide which is capable of acting as a primer

(see claim 1 in claim 19), "a blocking oligonucleotide, which would only serve to compete with the second primer of the primer pair of the subject invention (i.e., the primer comprising a moiety capable of quenching, masking or inhibiting) and thereby block primer extension" as argued by applicant is incorrect.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. No claim is allowed.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30

(November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CAR § 1.6(d)). The CM Fax Center number is (571)273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Frank Lu, Ph.D., whose telephone number is (571)272-0746. The examiner can normally be reached on Monday-Friday from 9 A.M. to 5 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571)272-0735.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

April 12, 2007

FRANK LU
PRIMARY EXAMINER